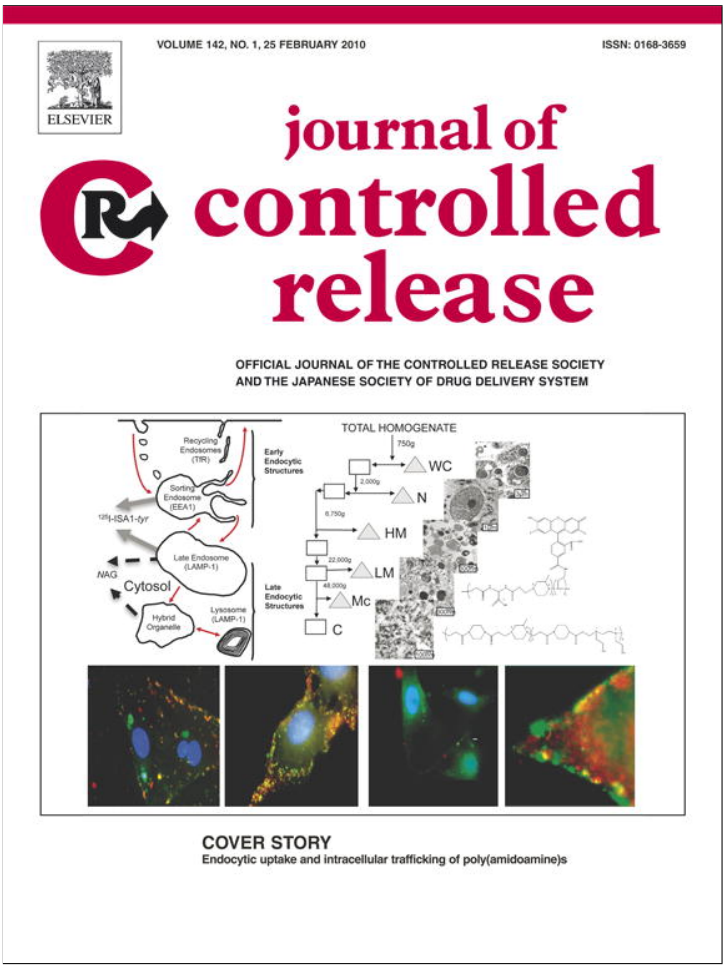

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Cover Story

Endocytic uptake and intracellular trafficking of poly(amidoamine)s

The ultimate goal of drug delivery is drug targeting, not only to a target tissue and cell, but also to an intended organelle inside the target cell. The drug targeting has become more important and demanding as new types of drugs emerge. Genomic and proteomic research is continuing to unravel the molecular basis of many diseases. This, in turn, is leading to an exponential increase in the number of putative macromolecular therapeutics, including small interfering ribonucleic acids (siRNAs), genes, proteins and peptides. Despite more than two decades of innovative research, however, in the majority of cases, delivery of macromolecules has been difficult, not to mention targeting. Delivery of nucleic acids is especially challenging due to their high charge density. Viral delivery systems have been effective but at the same time very dangerous. It has been difficult to develop safe non-viral vectors that are able to promote their efficient cell-specific targeting and intracellular delivery in the clinical setting. For drugs to be effective, they have to be delivered to the cytosol of the target cells. A key biological rate-limiting step for the development of effective biocompatible, polymer-based cytosolic delivery systems is their poorly efficient endosomal escape. This precludes efficient and reproducible intracellular delivery (cytosolic or nuclear) of the desired therapeutic dose.

The paper of Richardson et al. [1] in this issue deals with the endocytic uptake and intracellular trafficking of poly(aminoamine)s (PAA). A specific structure and salt form of PAA, identified as ISA1, displays pH-dependent conformational changes and membrane perturbation, leading to efficient endosomolysis and thus efficient intracytoplasmic delivery of drugs and genes. Richardson and his colleagues provide a direct evidence, for the first time, of the ability of an endosomolytic PAA to permeabilize endocytic vesicular membranes *in vivo*. Their study is distinguished from others by its thoroughness and unequivocal data in studying the endosomal escape of the PAA system. Radiolabelled PAA combined with liver sub-cellular fractionation was used to quantitate the dose- and time-dependant passage of the polymer along the endocytic pathway after intravenous administration. Quantitation of vesicle permeabilization by measuring the transfer of *N*-acetyl-β-D-glucosaminidase (NAG) from the vesicular fraction into the cytosolic fraction over time showed that increasing polymer dose enhanced escape of both radioactivity and NAG. These results were substantiated by the *in vitro* study examining the dose-dependent enhancement of NAG release from isolated vesicle containing the PAA. One of the important observations in the study is that PAA endosomolytic activity may be due to physical PAA–membrane interaction, rather than due to the proton sponge effect. Won et al. also pointed out previously that the adsorption of polycation molecules to endosome membranes may be required for the endosome lysis process [2].

The reported observations have more general implications for potential efficacy/toxicity of endosomolytic polymeric vectors per se. Moreover, the approach taken could be more widely applied to provide much needed "quantitative" information on the intracellular compartmentation of non-viral delivery systems and their therapeutic payload. Since successful endosomolysis followed by efficient intracytoplasmic delivery is required for all drug delivery systems, the approach used by Richardson's team can be useful in developing more efficient delivery vehicles for drug targeting in general.

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